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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,326	HOFFMAN ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007 and 13 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,8 and 10-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8 and 10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1, 4, 7-8 AND 10-25 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 1/3/2007 and the supplemental amendment filed 2/13/2007 and the Information Disclosure Statement filed 2/13/2007, (2 sheets), have been received and the appropriate papers, *i.e.*, those of 1/3/2007 and 2/13/2007, have been entered into the application. Accordingly, claims 1, 4, 7-8 and 10-16 have been amended; claims 2-3, 5-6 and 9 have been cancelled; and claims 17-25 have been added.

In light of the amendments, as well as the remarks of applicants at pages 10-11 of their amendment, the (i) objection to claims 11 and 13 and (ii) the rejections of the claims under 35 U.S.C. § 112, 2nd Paragraph, as set forth in the previous Office action dated January 9/1/2006 are overcome and thus are hereby *withdrawn*. However, upon further consideration, new grounds of rejection are being applied against the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112 (1st Paragraph)

Claims 1, 4, 7, 14-15, 17-20, 24 are newly rejected and claims 10, 12 and 16 remain rejected under 35 U.S.C. 112, 1st Paragraph (Written Description), for the reasons of record as set forth in the previous Office action dated September 1, 2006 at pages 4-5, which reasons are herein incorporated by reference.

Applicants' amendments and remarks at pages 12-15 of the amendment have been carefully considered, but fail to persuade the Examiner of error in maintaining the present rejection for the following reasons.

In attempting to overcome the present ground of rejection, applicants have remarked that the MPEP states that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species (MPEP § 2163 II.A.3.(a).ii). Examiner agrees with the applicants that description of a representative number of species satisfies the written description requirement for a claimed genus. However, this is not at issue in the present rejection. Applicants next submit that there are situations where even one species actually adequately supports a genus, citing, for example, *In re Herschler*, 591 F2d 693, 697, 200 USPQ 711, 714 (CCPA 1979). However, as applicants' counsel is certainly aware, the genus at issue in *In re Herschler* were "physiologically active steroid[s]" supported only by a single specie, corticosteroid. The court concluded that the written description only need be so specific as to lead one of ordinary skill in the art to that class of compounds. In the instant case, the claims still recite classes of compounds or "a precursor of said agent". While applicants have adequate written description for the general class of agents recited in the claims, they certainly do not have adequate written description for a "precursor" of said agents. Accordingly, the claims remain properly rejected.

Claims 1, 4, 7-8, 10-21 and 24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of tumors with disulfiram, BSO and carmustine, does not reasonably provide enablement for the treatment of tumors with the broad genera of agents contemplated by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of malignant tumors comprising administering combinations of agents that include: (i) agents that oxidize GSH; (ii) agents that form adducts of conjugates with GSH; (iii) agents that inhibit the GCS enzyme; (iv) agents that inhibit the GR enzyme; and (v) agents that diminish the precursor of GSH.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable

factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an

area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of malignant tumors with combination of active agents selected from broad genera of compounds defined only by biological activity. Others, such as claims 8 and 11, are narrower, reciting specific species of the claimed genera of compounds. All, however, are extremely broad insofar as they disclose the general treatment of malignant tumors with combinations of active agents selected from five broad genera of compounds defined only by biological activity.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. In fact, the specification is purely prophetic and theoretical in nature. Applicants theorize that the claimed combinations of active

agents will be useful in the treatment of tumors purely based on their individual mechanisms of action. The direction concerning treating tumors is found in the specification at pages 24-30, which merely states applicants' intention to do so by providing an *in vivo* assay for determining the tumor growth inhibitory effect of the claimed compounds. No compounds were actually tested in this assay. Applicants describe formulations at page 25, which only describes known routes of administration. Doses required to practice their invention are described at page 27, but only for three specific drugs (BSO, disulfiram, and carmustine). There is an *in vivo* assay described in pages 24-25 (with no data) and it is unclear if this assay correlates to all of the tumors encompassed by the claims. There is no working example of treatment of any tumor in cells, animals or man. While applicants define the nature of the claimed active agents, inhibition of an enzyme does not predictably correlate to clinical efficacy. Thus, there are no working examples correlating the biological activity of the claimed active agents with efficacy in the treatment of tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combinations could be predictably used as a treatment for all malignant tumor growth as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is

granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Cicuit 1997).

In the instant case, applicants have presented a general idea that apoptosis of malignant cells can be achieved by increasing the intracellular redox potential, *E*, above E_{CCP}, and maintaining this higher *E* for an appropriate duration of time such as to induce selective apoptosis of cancer cells. However, the claims encompass a multitude of compounds, defined only by biological activity, having a plethora of chemically and biologically distinct substituents. The idea that combining such compounds will, *a priori*, lead to an effective treatment of all malignant tumors is simply beyond the scope of the present invention.

Determining if any particular claimed compound or combination of compounds would treat any particular malignant tumor would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4, 7-8 and 10-25 are rejected under 35 U.S.C. § 102(a) as being anticipated by Hoffman (WO 02/056823) (cited by applicants in IDS filed 2/13/2007).

Hoffman teaches a method of treating malignancies through control of the redox state or environment of the cell, comprising administering a GSH-decreasing agent (Abstract). Treatment of tumors is taught at page 7, lines 25-32. GSH depleting agents include oxidizers of GSH (*e.g.*, α-lipoic acid, hydrogen peroxide, ascorbic acid, quinones), agents that form adducts with GSH (*e.g.*, Michael acceptors), and inhibitors of GSH (*e.g.*, BSO) (pages 9-10). These are the same agents recited in instant claims 1, 7, 8, 11, 13, 21-23 and 25. Combination with standard chemotherapeutics as recited in instant claim 4 is taught at page 11, line 30 to page 12, line 4. Hoffman teaches combinations comprising more than one GSH-depleting agent as recited in the instant claims (page 13, line 10 to page 14, line 6; page 16, line 5 to page 17, line 18; page 19, lines 11-33). With respect to the instantly claimed functional limitations (e.g., "such that" clauses in claims 1 and 17-18), it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied

on" (205 USPQ 594). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Accordingly, for the above reasons, the claims are deemed properly rejected.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 4, 7-8 and 10-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,589,987 (Issued July 8, 2003; Filed Sept. 8, 1999) in view of Huang *et al.* (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), Ali-Osman *et al.*

(Mol. Pharm., 1996, vol. 49, pages 1012-1020) and Nagendra *et al.* (Alcohol, 1994, vol. 11, pages 7-10).

The instant claims are drawn to the treatment of tumors comprising administering disulfiram (oxidizes GSH), buthionine sulfoximine (BSO; inhibits GCS enzyme) and carmustine (BCNU; inhibits GR enzyme). Applicants claim that administration of "at least two agents that decrease the $[GSH]^2/[GSSG]$ ratio" in the malignant cells of the tumor will lead to treatment of said tumor in a subject (see instant claim 1).

Applicants' remarks relevant to the instant issue at pages 17-21 of their amendment have been carefully considered, but fail to persuade the examiner of error in his determination of obviousness.

Applicants argue that the present specification establishes that *E* must be held above the threshold long enough so that all the cancer cells enter phase G_{1pm} of the cell cycle because that is where they will get trapped if *E* is above the threshold. Thus, it is a "very important aspect" of the invention that the decreased $[GSH]^2/[GSSG]$ ratio be maintained in the malignant cells continuously for about 15 to about 75 hours. Thus, applicants have offered that because the references do not teach or suggest that the $[GSH]^2/[GSSG]$ ratio be maintained in the malignant cells continuously for about 15 to about 75 hours, the present rejection is not proper. The examiner cannot agree that such provides a patentable distinction. See MPEP § 2144 under the heading, "Rationale Different From Applicant's is Permissible" where it is set forth that, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re*

Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972)". In both the prior art and the present claims, the ultimate treatment of tumors is or would have been expected. Also, in both the prior art and the present claims, the active agent(s) are administered in effective amounts to treat cancer and/or tumors.

Modifying administration regimens, doses, length of administration, etc. in order elicit optimal treatment of tumors are all well within the purview of the skilled artisan. Applicant's observation as to *why* the claimed combinations are effective is not an act of invention because applicants are not manipulating the active agents in any different manner than is taught and/or suggested by the prior art and do not provide for an ultimate effect that is not taught by or suggested by the prior art.

Accordingly, for the above reasons, the claims are deemed properly rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4, 7-8 and 10-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-20 and 25-28 of copending Application No. 11/596,043. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of inducing apoptosis in cancerous cells as claimed in the '043 application reasonably encompass the "treatment" of tumors as instant claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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AU 1614

April 26, 2007

Phyllis Spivack
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4/26/07